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## Music-based interventions in neurological rehabilitation

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# 1   **Music-based interventions in neurological rehabilitation**

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## 24   **Summary**

25   During the last ten years, an increasing number of controlled studies have addressed the  
26   rehabilitative effects of music-based interventions in several neurological diseases. While  
27   the amount of the studies and the level of evidence is highest in stroke and dementia,  
28   increasing evidence is accumulating for the effects of music-based interventions in  
29   Parkinson's disease, epilepsy, and multiple sclerosis. Studies have confirmed that  
30   interventions, such as music listening, singing, or playing an instrument, are beneficial for  
31   cognition, motor function, or emotional well-being in these patients. Although music-based  
32   interventions may target divergent functions, such as motor performance, speech, or  
33   cognition, the psychological effects and neurobiological mechanisms underlying the impact

34 of music are likely to share common neural systems for reward, arousal, affect regulation,  
35 learning, and activity-driven plasticity. Although further controlled studies are still needed  
36 to establish the clinical efficacy of music in neurological recovery, music-based  
37 interventions are emerging as promising rehabilitation strategies.

## 38 **Introduction**

39 The population is ageing rapidly and the number of persons suffering from severe age-  
40 related brain diseases is rising<sup>1</sup>. Less than 20% of the heavy economic burden of chronic  
41 brain diseases is due to acute treatment and care<sup>2,3</sup>. This has raised the need to pursue  
42 new cost-effective, light-input rehabilitation strategies, both independent of and  
43 complementary to traditional methods, such as physiotherapy, occupational therapy, or  
44 speech therapy.

45 Since neurogenesis in the adult brain has no clinically meaningful impact, brain recovery  
46 relies upon the spared neurons' ability to compensate for lost function by growing neurites  
47 and forming novel synapses to rebuild and remodel the injured networks<sup>4-8</sup>. This is thought  
48 to be achieved in traditional rehabilitation strategies by targeted training of the weakened  
49 function<sup>9-12</sup>. An alternative strategy would be to increase the overall level of brain activity  
50 through sensory and cognitive stimulation<sup>13</sup>.

51 Music listening improves neuronal connectivity in numerous specific brain regions of the  
52 healthy participants<sup>14-17</sup>, and musical activities, such as playing an instrument, promote  
53 neural plasticity, and induce changes in the grey matter and white matter<sup>18-20</sup>. Music has  
54 been shown to be efficacious in the recovery of postoperative patients by several outcome  
55 measures such as pain, anxiety, use of analgesics, and patient satisfaction,<sup>21</sup> suggesting  
56 that music might enhance neurological rehabilitation as well.

57 Formal music-based intervention, music therapy, can comprise of active interventions (e.g.  
58 music creating, instrument playing, singing, musical improvisation) and receptive  
59 interventions (e.g. music listening) administered by a credentialed music therapist.

60 Although a Cochrane review evaluating the effect of music interventions in acquired brain  
61 injury has been recently published<sup>22</sup>, a comprehensive overview on music-related  
62 interventions in the rehabilitation of the major neurological diseases, including  
63 degenerative diseases and other neurological entities in which the rehabilitative effect of  
64 music has been studied, is needed. Here, we appraise the randomized controlled trials

65 (RCTs) investigating the effects of music-based interventions in the rehabilitation of stroke,  
66 dementia, PD, epilepsy, and MS.

## 67 **Search strategy and selection criteria**

68 We searched PubMed up till April 11, 2017 using Medical Subject Headings (MeSH) for  
69 diseases “stroke”, “brain injuries”, “dementia”, “parkinsonian disorders”, “epilepsy”, and  
70 “multiple sclerosis”, combined with MeSH for “music” or “music therapy” and keywords  
71 “melodic intonation therapy”, “rhythmic auditory stimulation”, “rhythmic auditory cueing”,  
72 and “music supported therapy”. Additional references were gathered from reference lists  
73 and relevant articles. We included only the RCTs applying a minimum of one-week  
74 intervention, published in English over the past 10 years, except for two older landmark  
75 studies.

## 76 **Music-based interventions for stroke**

77 Stroke is the one of the leading causes of long-term disability in the world<sup>23</sup>. Of the major  
78 neurological entities, the strongest evidence for effectiveness of music-based interventions  
79 has been presented for stroke. We identified 16 RCTs utilizing music during recovery from  
80 stroke-related neurological and neuropsychiatric disturbances (Table 1)<sup>24–39</sup>. The  
81 parameters assessed included motor functions, such as gait and upper extremity  
82 function<sup>24,25,27,30,33–39</sup>, language functions<sup>26,28,29</sup>, cognitive functions, such as memory and  
83 attention<sup>28,32</sup>, mood<sup>28,32,34</sup>, or quality of life (QoL)<sup>30,34</sup>. The measurements were carried out  
84 with various standard motor tests (e.g., Fugl–Meyer assessment, the Box and Block Test,  
85 Berg Balance Scale, and Nine-Hole Pegboard Test), clinical neuropsychological  
86 assessments (e.g., CogniSpeed, Wechsler Memory Scale), standard language function  
87 assessments (e.g., Boston Diagnostic Aphasia Examination), and questionnaires (e.g.,  
88 Stroke Impact Scale, Profile of Mood States, and Stroke and Aphasia QoL Scale-39). In  
89 addition, computer-based movement analyses<sup>30,35,37,38</sup>, MRI analysis<sup>28,32,39</sup>,  
90 magnetoencephalography<sup>31</sup>, or electroencephalography<sup>33</sup> were utilized to assess motor  
91 performance and neuroplasticity. Metronome-like rhythmic stimulus was used in five  
92 studies on stroke-related motor paresis<sup>30,34,36,37,39</sup>. Favorite music selected through  
93 interview was used in three studies<sup>28,31,32</sup>. The genres of favorite music were not reported.  
94 Three studies used children’s songs and folk songs<sup>24,33,35</sup>. Five studies involved a trained  
95 music therapist<sup>26–28,31,32</sup>.

## 96    **Effects on motor symptoms**

97    Hemiparesis is the most common consequence of stroke, affecting over 70% of the  
98    patients<sup>40</sup>. In total, eight studies reported enhanced motor recovery when stroke patients  
99    were rehabilitated with music<sup>25,27,30,33–37</sup>. Four of these studies investigated the use of  
100    rhythmic auditory stimulation (RAS) in gait training and all found it to improve gait  
101    parameters more than gait training without any musical support<sup>30,36–38</sup>. In RAS, external  
102    auditory cues guide movement through anticipated temporal sequence, the frequency of  
103    which is adjustable and gradually entrains the movement. Across studies, significant  
104    improvements with small (Cohen's  $d \geq 0.2$ ), medium ( $d \geq 0.5$ ), or large ( $d \geq 0.8$ ) effect  
105    sizes (Table 1) were observed in gait velocity, stride length, length of foot contact to  
106    surface, cadence, and asymmetry after 3-6 weeks of RAS compared to conventional  
107    training without RAS<sup>36–38</sup>. Similar findings were reported when intensive gait training with  
108    RAS was investigated with respect to postural control and gait performance in chronic  
109    stroke patients<sup>30</sup>. In 6 weeks, RAS group improved in balance, gait velocity, cadence,  
110    stride length, and double support period on the affected side<sup>30</sup>. When RAS was utilized in  
111    the form of combining rhythmic music with movement therapy, stroke patients showed  
112    improved ankle and arm movement after 8 weeks of intervention, with medium and large  
113    effect sizes, respectively<sup>34</sup>. One study compared bilateral arm training with RAS to dose-  
114    matched therapeutic exercises, but found no significant differences between the groups<sup>39</sup>.  
115    Interestingly, RAS intervention conducted by a music therapist resulted in greater  
116    improvement compared to studies conducted by a non-music therapist<sup>22</sup>.

117    Music-supported therapy (MST), in which musical instruments (electric drum pads and  
118    keyboards) are used to train gross and fine movements of the hemiparetic upper extremity  
119    by playing simple melodies, was found to be effective in rehabilitating the arm paresis after  
120    stroke in five RCTs<sup>24,25,27,33,35</sup>. Three weeks of MST improved motor skills of the paretic  
121    arm significantly more than conventional physiotherapy, an effect shown by several  
122    validated clinical tests with small to medium effect sizes<sup>33,35</sup>. The effects were  
123    accompanied by improved cortical connectivity and increased activation of the motor  
124    cortex<sup>33</sup>. These effects seem to be specifically caused by music rather than motor training  
125    per se, since patients practicing with mute instruments remained inferior to the music  
126    group<sup>27</sup>.

127    One study utilized movement sonification therapy, a recent development in MST<sup>25</sup>. Gross  
128    movement was transformed into sound, providing continuous feedback, substituting for

129 defective proprioception. Sonification therapy reduced joint pain and improved smoothness  
130 of movement more than movement therapy without sound with large effect sizes. Delayed  
131 auditory feedback in MST has been proposed to be as effective as the traditional  
132 immediate auditory feedback<sup>24</sup>. While both RAS and MST involve auditory-motor coupling,  
133 incorporating full music stimulus might result in additional enhancement due to the  
134 personal motivational value of music. Internal synchronization, based on musical memory,  
135 generates expectation of consecutive sounds of a familiar song and provides precise  
136 mental timing feedback for movement, thus supporting the patient's impaired  
137 proprioception.

### 138 **Effects on aphasia**

139 Aphasia affects around 30% of stroke patients<sup>40</sup>. In two RCTs, active music therapy  
140 improved the speech of chronic aphasics<sup>26,29</sup>. In one of them, Melodic Intonation Therapy  
141 (MIT)<sup>41</sup>, a singing-based speech therapy designed for non-fluent aphasics, was applied on  
142 subacute aphasics<sup>29</sup>. MIT is a formalized treatment to transform the prosody of speech into  
143 low and high pitches – which the patient then learns to use to intone the stressed and non-  
144 stressed syllables, respectively – accompanied by rhythmic tapping with the left, non-  
145 paretic hand on each syllable. Training starts with two-syllable words and proceeds  
146 gradually to phrases. MIT improved the daily life communication and object naming  
147 significantly more than the control group receiving other types of language rehabilitation  
148 with medium and large effect sizes, respectively<sup>29</sup>. Music-related speech therapy, MIT in  
149 particular, is conceptually elegant and music therapy interventions may be more effective  
150 in aphasia than speech training without music<sup>22</sup>.

### 151 **Effects on cognitive and emotional deficits**

152 Deficits in cognitive functions (e.g., memory, attention, executive function) and mood (e.g.  
153 depression) affect around 30-50% of stroke survivors<sup>42,43</sup>. In one RCT, one-hour daily  
154 listening to favorite music selected with the help of a music therapist and continued during  
155 the first two post-stroke months enhanced cognitive recovery<sup>32</sup>. In a 6-month follow-up, the  
156 music group still showed significant improvements with large effect sizes in performance of  
157 tasks measuring verbal memory and focused attention compared to a control intervention  
158 (audio book listening) or standard care<sup>32</sup> (see Figure 1A). Compared to standard care,  
159 music listening was also associated with less depression and confusion with medium  
160 effects<sup>32</sup> (see Figure 1A). The cognitive gains induced by music listening were associated

161 with enhanced auditory memory-related function in temporal brain areas<sup>31</sup> and increased  
162 gray matter volume in spared prefrontal regions<sup>28</sup> (Figure 1B-C). Music-induced reduction  
163 in negative mood was linked to increased grey matter volume in limbic areas<sup>28</sup>. In addition  
164 to music listening, RAS therapy improved patients' mood but with non-significant effect  
165 size<sup>34</sup>. Although the long-lasting positive effects were shown by several outcome  
166 measures, these effects need to be replicated.

## 167 **Music-based interventions for dementia**

168 The most common etiologies of dementia are Alzheimer's disease, cerebrovascular  
169 diseases, and their combination. In these entities, neural degeneration progresses over  
170 several years leading sequentially to memory problems and other behavioral disturbances.  
171 Altogether 17 RCTs on persons with dementia (PWDs; Table 1) have assessed the effects  
172 of music intervention on neuropsychiatric and behavioral symptoms, such as anxiety, and  
173 agitation (14 studies)<sup>44–57</sup>, depression (six studies)<sup>47,49,55,58–60</sup>, cognitive status (five  
174 studies)<sup>47,49,51,58,59</sup> as well as on QoL (four studies)<sup>46,47,59,60</sup>. Neuropsychiatric and  
175 behavioral symptoms were assessed with tests, rating scales, or questionnaires  
176 measuring overall symptom severity (e.g., Neuropsychiatric Inventory (NPI), Cohen-  
177 Mansfield Agitation Inventory, Behavior Pathology in Alzheimer's Disease Rating Scale),  
178 depression (e.g., Cornell Scale for Depression in Dementia, Geriatric Depression Scale),  
179 cognitive status [e.g. Mini-Mental State Examination (MMSE), Severe Impairment Battery),  
180 and QoL or well-being (Cornell-Brown Scale for QoL in Dementia, Dementia Care  
181 Mapping). Most interventions used vocal or instrumental music presumably familiar to the  
182 PWDs, such as personal favorites, all-around popular music or common children's songs.  
183 All studies except for one involved a music therapist.

## 184 **Effects on cognitive deficits**

185 Music listening coupled with cognitive elements (reminiscence, attention training) or  
186 physical exercise improved overall cognitive performance (measured by MMSE) of  
187 patients with dementia compared to standard care in four studies published by three  
188 separate groups<sup>47,51,58,59</sup>. The effect sizes varied from small to medium. In addition,  
189 improved performance in these music interventions was reported for tests measuring  
190 attention and executive functions (small to medium effect size)<sup>51,59</sup>, orientation (medium  
191 effect size)<sup>59</sup>, and verbal or episodic memory (medium effect size)<sup>51,59</sup>. In one RCT, also  
192 caregiver-implemented singing was found to enhance working memory with medium effect

size, especially in mild dementia and also to reduce caregiver burden as shown by a large effect size<sup>59</sup>. On the contrary, no significant changes in cognitive performance were observed for group-based music and cooking interventions in persons with moderate-severe dementia<sup>49</sup>. The cognitive benefits of music in the early stages of dementia may be related to enhanced cognitive reserve, the utilization of alternative networks and cognitive strategies to cope with advancing pathology<sup>61</sup>.

### **Effects on neuropsychiatric symptoms, mood, and quality of life**

Six studies found music therapy to be effective in improving the neuropsychiatric symptoms of dementia with medium to large effect sizes<sup>44,46–48,54,56</sup>. Three studies assessed the carry-over effect<sup>44,55,58</sup>, which varied from less than four weeks to two months. In contrast, two studies failed to show any significant effect of music therapy or music listening on neuropsychiatric symptoms<sup>45,49</sup>. The music intervention program resulted also in improved PWD-caregiver interaction and well-being of the PWDs (large effect size)<sup>46</sup>. Regarding specific neuropsychiatric symptoms, two studies showed music to reduce anxiety and agitation in PWDs<sup>52,55</sup>, but their effect sizes diverged. In contrast, four RCTs found music to be ineffective in reducing anxiety or agitation<sup>50,51,53,57</sup>.

QoL was assessed in three studies<sup>47,59,60</sup>. While Cooke et al. (2010) did not find any significant differences between the effects of music and control (reading) interventions<sup>60</sup>, Särkämö et al. (2014) reported that music listening compared to standard care increased QoL significantly and with large effect size<sup>59</sup>. Music listening was found especially beneficial in moderate dementia with etiology other than Alzheimer's disease<sup>47</sup>. Improvement of mood in PWDs has been reported in four studies, effect sizes varying between small and large<sup>47,55,58,59</sup>. Two other RCTs failed to show such an effect<sup>49,60</sup>. Overall, the effects of musical interventions in dementia may be driven by the comfort and emotional safety induced by familiar music, which can temporarily overcome the confusion and disorientation by anchoring attention on a positive familiar stimulus in an otherwise confusing environment. This anchoring effect may be enhanced by using headphones. Familiar music is also imbued with personal emotions, which can trigger autobiographical memories and help to restore a sense of identity for a while.

### **Music-based interventions for Parkinson's disease**

Parkinson's disease (PD) is primarily a movement disorder due to degeneration of dopaminergic nigro-striatal tract. In addition, the early phase of PD includes autonomic



nervous system and other non-motor deficits, and 30% of the patients develop dementia-level cognitive decline in the late phase<sup>62</sup>. Effects of music on several symptoms and signs of PD have been studied in five RCTs (Table 1)<sup>63–67</sup>. Four studies examined the effects of music-assisted motor training using motor parameters as outcome measures<sup>63–66</sup>. Two studies<sup>63,67</sup> evaluated non-motor parameters, QoL, cognition, or social parameters. In all trials, medication remained unchanged during the interventions.

General motor performance was assessed by motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III), and specific motor functions by e.g. Berg Balance Scale and 6-minute walk test. Specific gait parameters were analyzed using video recordings and computer-assisted motion analysis programs. QoL was evaluated using validated questionnaires. Music used in the intervention varied from rhythmic auditory cueing to self-selected favorite music. The genres of the patient's favorite music were not reported. Only one study involved a music therapist<sup>63</sup>.

Based on effect sizes calculated from the reviewed data, the most coherent and clinically significant beneficial effect on motor symptoms was produced by dancing. Compared to the standard care, both tango and waltz or foxtrot intervention groups improved in balance, 6-minute walk test, and backward stride length with large effect sizes<sup>65</sup>. In a smaller study, tango improved balance with large effect<sup>66</sup>. Dancing also improved overall mobility with large effect size<sup>67</sup>. Bearing a close analogy to dancing, music therapy with rhythmic movements<sup>63</sup> improved overall mobility in patients with PD. Gait training synchronized to music resulted in improved velocity, stride time, and cadence with large effect sizes compared to the control group<sup>64</sup>. Both studies reported reduction in PD specific motor symptoms (medium effect size)<sup>63,64</sup>.

Two studies found music-based intervention to improve QoL with large effect size<sup>63,67</sup>. Dancing tango appeared to be significantly more effective than waltz, Tai Chi or regular treatment<sup>67</sup>. In addition, patients reported better social support after the intervention. Improvements in cognition have been reported in one study<sup>63</sup>.

Although the sample sizes were relatively small, the reviewed evidence suggest that dancing and music-based interventions that synchronize movement to music can be beneficial in maintenance of motor performance in this slowly progressing disease. Rhythmical use of musical stimulus compensates for the failing control by the extrapyramidal system and enhances audio perception and movement

synchronization<sup>30,36,37</sup>. The perceived rhythm in music activates the neural circuits involved in motor actions and act as an external cue for movement thus replacing the impaired internal timing function in PD<sup>68</sup>. The use of music as stimulus may be more effective than auditory stimulation without music (e.g. metronome beat) in gait rehabilitation, as shown in stroke<sup>22</sup>. This might also explain the positive effects of dancing in PD. Furthermore, the improvement in motor control and possible decrease in disease specific symptoms could in turn improve the QoL. In all of studies reviewed, the follow-up period was too short to allow conclusions on the long-term effects of music interventions. The effects of music on the autonomic disturbances in PD have not been addressed in controlled studies.

## **Music-based interventions for multiple sclerosis**

Multiple sclerosis (MS) is one of the most common severe neurological disease in the young adult population. Despite relatively low prevalence, it bears need for expensive medication and long-lasting rehabilitation<sup>3</sup>. MS treatments aim to ameliorate function after flare-up of an MS-episode or to prevent new episodes. Only two RCTs<sup>69,70</sup> (Table 1) have studied the effect of musical interventions in alleviating the manifestations of MS. Between the studies, outcomes were different, and only one study involved a music therapist.

The RCT without music therapist included 19 patients and studied the effect of keyboard playing (audible vs. mute) in hand functionality<sup>69</sup>. Audible keyboard playing improved the functional use of the hand significantly with medium effect size, indicated by a questionnaire. Using a computerized gait analysis, a feasibility study on ten MS patients with gait problems found RAS to be effective in decreasing double-support time with large effect size<sup>70</sup>. While decreased double-support time may reflect improved dynamic balance<sup>71</sup>, none of the several other gait parameters differed from controls receiving standard care. The results of music-based interventions in MS are scanty and allow no definite conclusions on the rehabilitative effect of music. Although designing studies may be challenging due to diversity of MS deficits, motor functions, spasticity, fatigue, cognitive deficits, and mood might be feasible outcome measures in the future studies.

## **Music-based interventions for epilepsy**

Epileptic seizures arise from abnormal synchronization of electrical activity in the brain, and the most of them cease spontaneously by largely unknown mechanisms. Exposure to patterned auditory stimuli provides a noninvasive excitatory stimulation of the cortex, which

288 has been suggested to reduce epileptiform activity<sup>72</sup>. In this vein, one RCT (N=73; Table 1)  
289 has examined the effectiveness of music in epilepsy<sup>73</sup>. Patients were exposed to Mozart's  
290 music periodically every night for a year and a significant 17% reduction in seizure  
291 frequency was detected during the study period. In addition, a carry-over effect of 16%  
292 reduced seizure frequency persisted for one year. While no other RCTs on adult  
293 population have been published, a recent meta-analysis of 12 studies including both  
294 pediatric and adult patients with epilepsy of any kind indicated that 130 out of 153 patients  
295 respond favorably to music, the average reduction in interictal epileptic activity being 31%  
296 and 24% during and after the listening period, respectively<sup>74</sup>. Further studies are definitely  
297 needed, since all but two studies lacked a separate control group.

## 298 **Mechanisms underlying the rehabilitative effect of music**

299 Specific pathologies of the diseases evaluated here may affect, sometimes critically, the  
300 way the patient's brain processes music, and diverse manifestations of the diseases  
301 influence the selection of feasible music intervention. Considering the widely varying  
302 nature of the diseases in which music has led to improved recovery, enhanced  
303 rehabilitation, or alleviation of symptoms, several distinct explanatory mechanisms can be  
304 postulated.

### 305 **Neural activation and neuroplasticity**

306 Functional neuroimaging studies have shown that music induces widespread activation of  
307 the brain<sup>14–17</sup> (Figure 2), and correspondingly increases blood flow through the medial  
308 cerebral artery due to autoregulation<sup>75</sup> (Figure 3). This should provide favorable  
309 circumstances for recovery processes in general regardless of their nature, as for example  
310 after stroke, neuroplastic changes associated with functional recovery are activity-  
311 dependent<sup>76</sup>. Musical activities bear similarity to the concept of enriched environment  
312 which facilitates recovery at behavioral and neurobiological levels in animal models of  
313 many neurological illnesses<sup>13</sup>.

314 Given that active music-based rehabilitation involves multiple components analogous to  
315 musical training and music learning (i.e. iterated practice of movements coupled with  
316 auditory feedback and extensive cognitive processing), it is plausible that music-based  
317 neurological rehabilitation induces similar structural and functional neuroplastic changes  
318 as musical training<sup>18,19</sup>. Indeed, individual studies have reported memory-related plastic  
319 effects after mere music listening in recovering stroke patients<sup>28,31</sup> as well as neural

320 reorganization after MST<sup>33</sup>. Supporting literature has provided further evidence of  
321 neuroplasticity after MST<sup>77-79</sup> and MIT<sup>80</sup> in stroke patients.

322 In general, the specific cellular mechanisms of neuroplasticity remain unknown. While  
323 significant neurogenesis in elderly individuals seems unlikely, other putative mechanisms  
324 include neuronal hypertrophy, increased volume of neuropil, and changes in the vascular  
325 or glial compartments. An intriguing question would be to investigate, whether previous  
326 music exposure during a specific period of lifetime affects the plasticity of recovering brain.  
327 The possibility of negative plastic changes due to overly intense and/or premature  
328 intervention should be considered.

### 329 **Activation of reward, arousal, and emotion networks**

330 Music activates the dopaminergic mesolimbic system which regulates memory, attention,  
331 executive functions, mood, and motivation<sup>81</sup> (Figure 3). A key part of this reward system is  
332 the nucleus accumbens, which regulates mood and experienced pleasure. Its activation by  
333 intense emotional response ("chills") to music leads in healthy subjects to increased  
334 dopamine secretion directly proportional to the intensity of the experience<sup>81</sup>. This may  
335 partly explain the cognitive-emotional gains induced by music also in neurological patients.  
336 It is feasible to postulate that music-induced improvement of mood, arousal, and relief of  
337 confusion may enhance recovery of cognitive functions in neurological patients. Music-  
338 induced activation of the parasympathetic and inhibition of the sympathetic nervous  
339 system in PWDs, and corresponding changes in catecholamine and cytokine secretion has  
340 been considered as a soothing effect of music<sup>82</sup>. This is also a possible mechanism behind  
341 the effect of music ameliorating neuropsychiatric symptoms in dementia.

342 Music also produces measurable cardiovascular and endocrine responses indicated by  
343 lowered serum cortisol levels and inhibition of cardiovascular stress reactions<sup>82,83</sup> (Figure  
344 3). In animal models, prolonged stress can have maladaptive effects on neuroplasticity,  
345 such as dendritic atrophy, synapse loss, and decreased hippocampal neurogenesis<sup>84</sup>. In  
346 patients, elevated cortisol level in acute stroke correlates with increased infarct volume,  
347 and increases the risk of depression, poor prognosis, and fatal outcome<sup>85</sup>. We speculate  
348 that listening to music lowers stress hormone secretion in acute stroke, as it does in  
349 postoperative patients<sup>86,87</sup>.

350 Overall, neurological diseases and mood disorders have a high comorbidity, ranging from  
351 20% to 50%<sup>88,89</sup>. Common clinical experience is that depression diminishes adherence to  
352 rehabilitation, and published studies indicate that depression impairs functional outcome,  
353 QoL, and increases mortality<sup>90</sup>. According to the data reviewed here, music improved  
354 mood or diminished anxiety in PWDs<sup>52,59</sup> and stroke patients<sup>32,34</sup>. We conclude that music  
355 interventions are viable in improving the mood of neurologic patients. Yet, the causal  
356 relationship between music-induced mood improvement and neurological outcome still  
357 remains to be proved.

### 358 **Activation of alternative or spared neural networks**

359 Some music interventions allow access to an impaired function by engaging specific  
360 regions associated with musical rhythm, movement, singing, or memory<sup>68</sup>. Rhythmic  
361 entrainment, our inherent tendency to time movements to the regular beat of music, which  
362 forms the basis of RAS and playing-based music interventions, is based on the strong  
363 connectivity between the auditory system and motor system<sup>14</sup>. In diseases in which the  
364 internal sequencing and monitoring of actions is not working due to the dysfunction of the  
365 motor system, rhythmic entrainment can act as an external timer, cueing the execution of  
366 movements<sup>68</sup>. For instance, a stroke patient with impaired muscle coordination or a  
367 Parkinson patient with stiffness and bradykinesia may find it easier to execute motor tasks  
368 with rhythmic support provided by music listening or dancing<sup>30,36–38,63–66</sup>.

369 Singing, which is the key component of MIT, engages frontotemporal language and vocal-  
370 motor regions more extensively and bilaterally compared to speaking<sup>91,92</sup>. This enables  
371 training of speech in aphasia via both spared left hemisphere regions and homologous  
372 right hemisphere regions. The preserved ability to sing in aphasia has been reported as  
373 early as 1745, when a stroke patient with severe aphasia was reported to be only able to  
374 verbalize “yes”, but was able to correctly sing familiar hymns producing both the melody  
375 and the text of the songs<sup>93</sup>.

376 Familiar music specifically activates the anterior cingulate and medial prefrontal cortex in  
377 the healthy brain, suggesting that they are important in musical memory<sup>94</sup>. In persons with  
378 Alzheimer’s disease, the medial prefrontal cortex degenerates more slowly than other  
379 cortical regions and the regions that encode musical memory also show only minimal  
380 atrophy or decrease in glucose metabolism despite visible amyloid-beta accumulation<sup>94</sup>.

381 These observations provide a potential explanation why Alzheimer patients are able to  
382 recognize and respond emotionally to familiar songs even at late stages of the disease<sup>94</sup>.

## 383 **Conclusions and future directions**

384 Acute care and treatment accounts for a substantial proportion of costs associated with  
385 neurological diseases, and therefore, study of novel rehabilitation strategies to replace or  
386 complement traditional methods is warranted. With this aim, the effects of music-based  
387 rehabilitation in major neurological disorders have been studied in 41 RCTs. Music  
388 interventions seem to be beneficial particularly in motor rehabilitation in PD and stroke.  
389 Additionally, music interventions can have favorable effects on cognition, mood, and QoL  
390 in stroke and dementia.

391 Although the majority of the reviewed studies have reported positive effects, the possibility  
392 of publication bias should be considered. In addition, only few of the primary outcomes  
393 have been studied repeatedly. Limitations involved in most studies arise from small  
394 sample sizes and methodological heterogeneity in study design and in the interventions  
395 and outcome measures used across studies. In most studies, the duration of the music-  
396 induced rehabilitation effect was not systematically evaluated and is still largely unknown.  
397 Thus far, music-based interventions have been observed to have long-term effects in  
398 stroke (3 months)<sup>32</sup>, dementia (max. 2 months)<sup>44,55,58</sup>, and epilepsy (12 months)<sup>73</sup>.

399 In some studies, the difference between active and receptive intervention as well as the  
400 role of the music therapist (if participating) remained unclear. The therapeutic relationship  
401 inherent in formal music therapy is likely to have an additional impact on the outcome.  
402 While this aspect is difficult to delineate from the music intervention used, the outcome of  
403 an intervention given by a music therapist may in some cases be superior to that given by  
404 another health-care professional, as has been observed for RAS in gait rehabilitation<sup>22</sup>.  
405 However, the studies reviewed here showed that both music therapy and other music-  
406 based interventions have beneficial effects. Most of the studies lacked adequate  
407 description of the music type used. As music types can greatly vary (e.g. stimulating vs.  
408 soothing), the expected effects on physiological parameters, arousal, and affect regulation  
409 differ. Furthermore, most of the reviewed studies did not use patient-selected or favorite  
410 music. Concerning the strong emotional components of musical experience, using patient-  
411 selected music would be beneficial as it is meaningful and rewarding to the patient.

412 More high-quality intervention studies, particularly large-scale trials, such as cluster-  
413 randomized multicenter RCTs, where the established music interventions are embedded  
414 into the clinical rehabilitation practice, would be needed to establish their efficacy and the  
415 real-life applicability. For better comparability of the studies, it would also be important to  
416 use common outcome measures, clearly document the type of the intervention (active vs.  
417 receptive), and music used (patient-selected vs. experimenter-selected) as well as define  
418 the optimal timing and length of the music interventions and determine the long-term  
419 duration of their rehabilitation effects. In addition, multimodal studies combining behavioral  
420 outcome measures with neuroimaging and neuroendocrinological markers are needed to  
421 determine specific neurophysiological mechanisms and effects of various music-based  
422 interventions in neurological patients.

423 Analysis of the amount of core therapeutic activities received, such as physiotherapy and  
424 occupational therapy, suggests that stroke patients receive only approximately 60% out of  
425 the recommended rehabilitation<sup>95</sup>. Scarceness of rehabilitation resources is likely to exist  
426 in most neurological wards. Thus, there is room for music interventions that are widely  
427 available and could easily be realized with minimal investments. These include self- or  
428 caregiver-implemented musical activities, such as music listening, and group-based  
429 musical interventions, such as group singing or dancing.

430 In future, mobile music applications (e.g., music streaming, games) as well as novel  
431 music-based rehabilitation technology utilizing virtual reality or adaptive music stimulation  
432 systems tailored for motor rehabilitation, will play an increasing role in bringing music to  
433 neurological patients, in both hospital, community, and home environments.

## 434 **Contributors**

435 A.J.S, V.L., and S.S. searched and reviewed the literature, A.J.S. created figures and  
436 tables, A.J.S. and S.S. wrote the primary manuscript, which was circulated among the  
437 other authors T.S., E.A., M.T. and V.L. All made significant additions based on their  
438 special areas of interest, which were incorporated into the final manuscript.

## 439 **Declaration of interests**

440 The authors have no conflict of interest to declare.

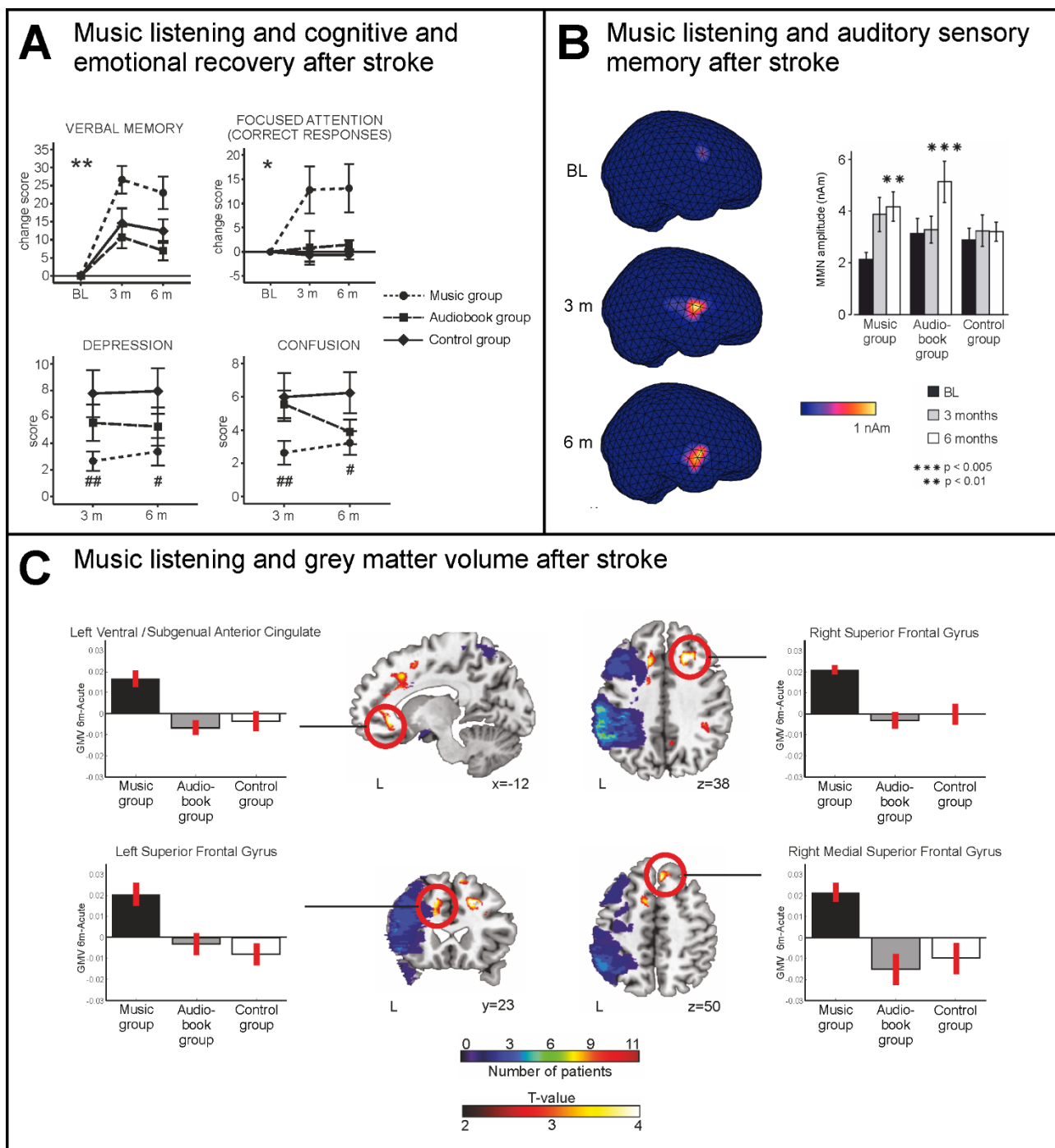
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446 Programme of Psychology, Finland.

## 447 **Figures and tables**

448 Figure 1 Cognitive, emotional and neural effects of daily music listening (Music group),  
449 audio book listening (Audio book group), and standard care (Control group) 1 week  
450 (baseline, BL), 3 months (3 m) and 6 months (6 m) after stroke. **(A)** Neuropsychological  
451 results (mean  $\pm$  SEM) showing improved recovery of verbal memory and focused attention  
452 (baseline score subtracted from the values) and less depression and confusion in the  
453 Music group compared to the Audio book and Control groups. \*\* $P < 0.01$ , \* $P < 0.05$  by  
454 mixed-model ANOVA. ## $P < 0.05$ , # $P < 0.1$  by one-way ANOVA. Adapted from Särkämö  
455 et al. 2008. **(B)** Magnetoencephalography (MEG) group results (mean  $\pm$  SEM) showing  
456 increased right hemisphere mismatch negativity (MMN) responses to pitch changes in the  
457 Music and Audio book groups compared to the Control group. Adapted from Särkämö et  
458 al. 2010. **(C)** Voxel-based morphometry (VBM) results of MRI data from left hemisphere-  
459 damaged patients (lesion areas in blue-green) showing larger grey matter volume (GMV)  
460 increases (mean  $\pm$  SEM) in prefrontal and limbic areas in the Music group compared to the  
461 Audio book and Control groups. Results are shown at  $p < 0.01$  (uncorrected) with  $\geq 50$   
462 voxels of spatial extent. L = left hemisphere. Adapted from Särkämö et al. 2014.

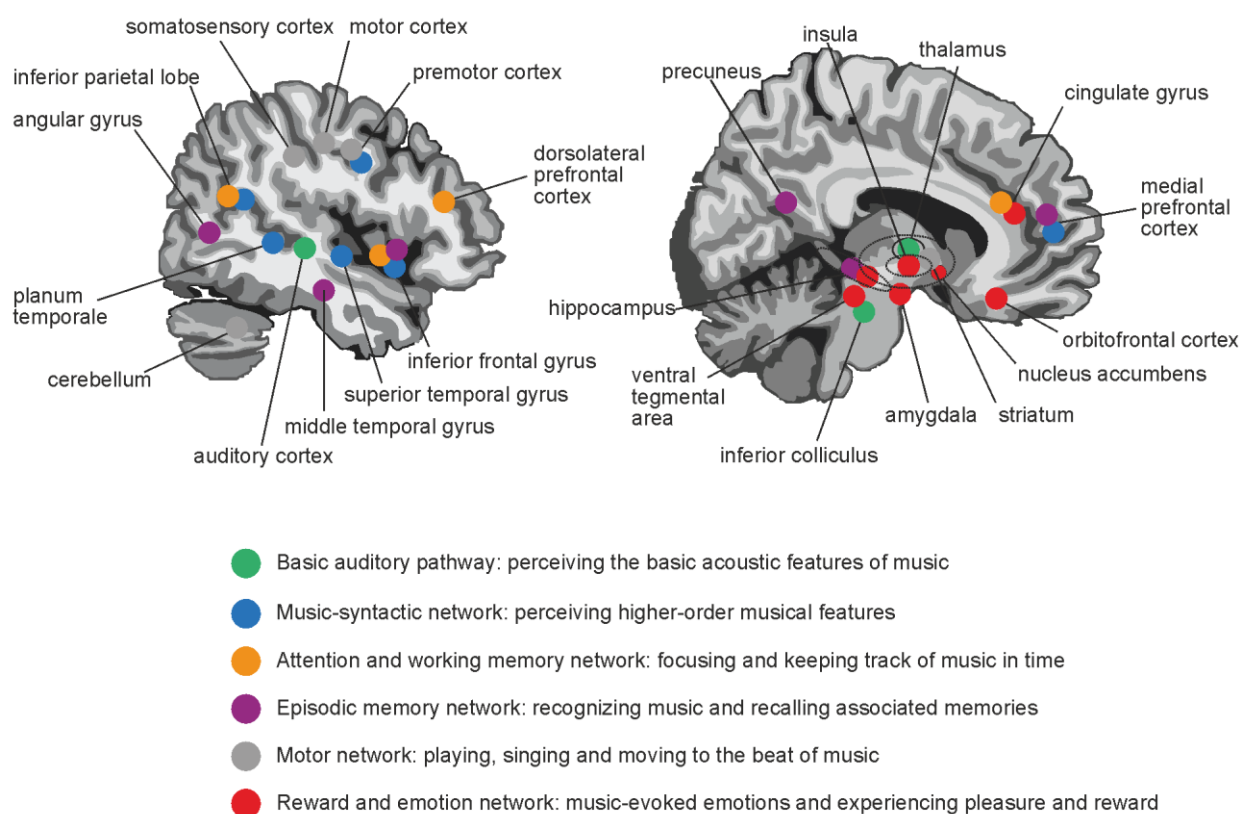




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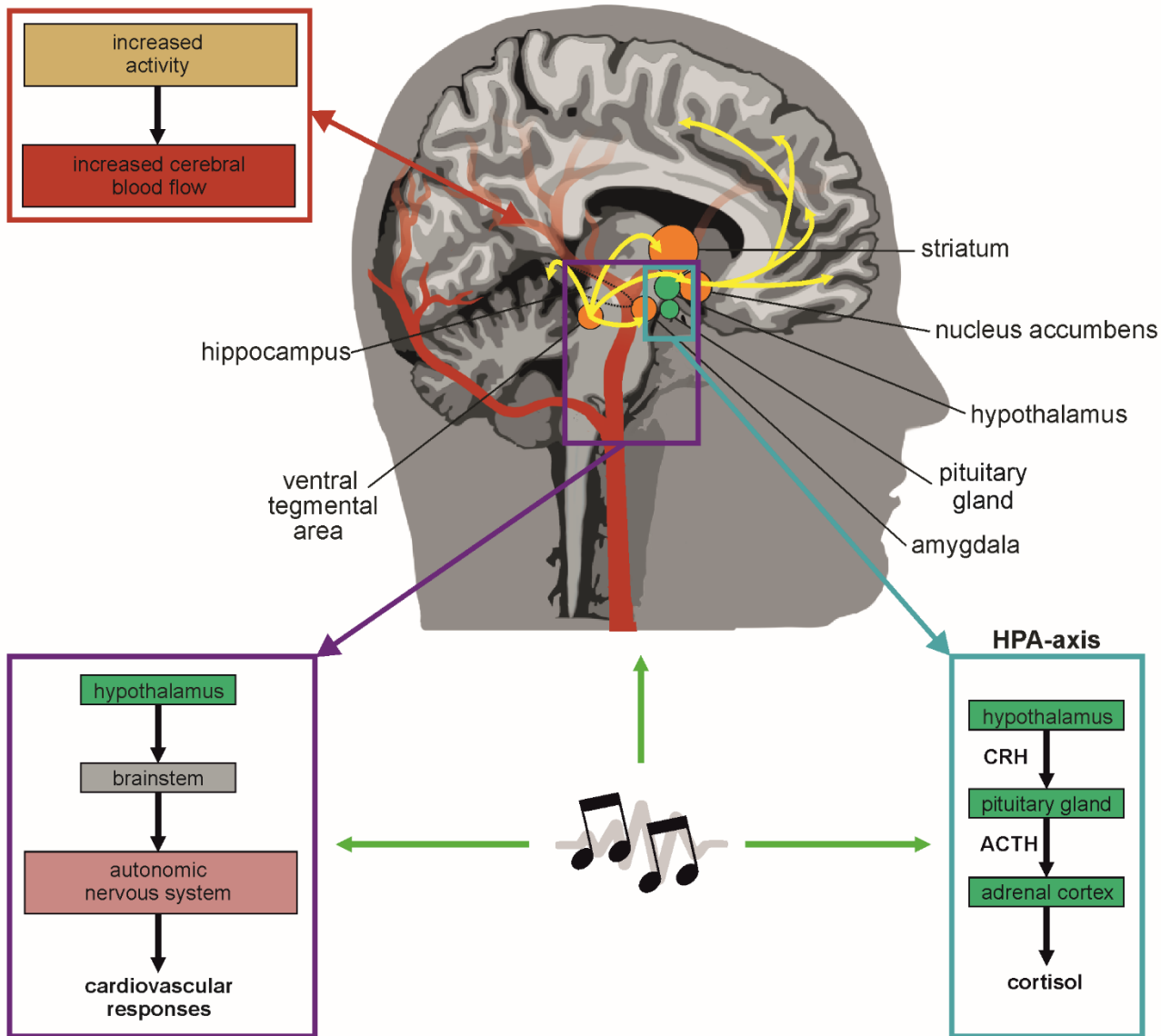
465 Figure 2 Schematic illustration of key brain areas associated with music processing-  
 466 based neuroimaging studies of healthy subjects. Note that although the image displays the  
 467 lateral and medial parts of the right hemisphere, many musical subfunctions are actually  
 468 largely bilateral (with the exception of pitch and melody processing, which are lateralized,  
 469 the activity in the right hemisphere being dominant). Adapted from Särkämö et al. 2013.



470

471

472 Figure 3 Schematic illustration of possible neurobiological mechanisms for underlying  
 473 the rehabilitative effect of music. Orange circles and yellow arrows represent the  
 474 mesolimbic system, and the green circles represent the hypothalamic–pituitary–adrenal  
 475 axis (HPA-axis). ACTH = Adrenocorticotrophic hormone, CORT = Cortisol, CRH =  
 476 Corticotropin-releasing hormone.



478 Table 1 Study characteristics.

	Number of participants	MT involved	Blinding	Study design / Primary outcome	Overall intervention time	Main results
STROKE						
van Vugt et al. (2016) <sup>24</sup>	34	No	Single	MST vs. MST with delayed sound / Hand movement.	5 hours in 4 weeks	There were no significant differences between the groups.
Scholz et al. (2016) <sup>25</sup>	25	No	No	Sonificated movement vs. movement without sound / Gross motor function.	10 days	Sonification therapy reduced joint pain ( $p < 0.05$ , $d = 1.96$ ) and improved movement smoothness ( $p = 0.04$ , $d = 1.16$ ).
Raglio et al. (2016) <sup>26</sup>	20	Yes	No	Singing, playing instruments, improvisation vs. speech therapy / Speech parameters in chronic aphasics.	22.5-37.5 hours in 15 weeks	Music therapy improved spontaneous speech ( $p = 0.020$ , $d = 0.35$ ).
Tong et al. (2015) <sup>27</sup>	33	Yes	No	MST vs. playing mute instruments / Upper-limb motor function.	20 sessions in 4 weeks	MST improved motor functions ( $p = 0.039$ ).
Särkämö et al. (2014) <sup>28</sup>	49	Yes	Single	Favourite music vs. standard care / Grey matter changes associated with cognitive improvement.	60 hours in 8 weeks	Music listening increased gray matter volume in frontal areas, limbic areas, and right ventral striatum. Reorganization in the frontal areas correlated with enhanced recovery of verbal memory, focused attention, and language skills, whereas the limbic area reorganization correlated with reduced negative mood.
van der Meulen et al. (2014) <sup>29</sup>	27	No	Single	MIT vs. other language intervention / Speech parameters in nonfluent aphasics.	30 hours in 6 weeks	MIT improved the daily life communication ( $d = 0.76$ ) and object naming ( $d = 1.73$ ).
Cha et al. (2014) <sup>30</sup>	20		No	RAS vs. intensive gait training / Postural control and gait performance.	15 hours in 6 weeks	RAS improved balance, gait velocity, cadence, stride length and double support period on the affected side, and in stroke-specific quality of life scale.
Whitall et al. (2011) <sup>39</sup>	92	No	Single	BATRAC vs. normal exercise / Functional reorganization and outcome.	18 hours in 6 weeks	There were no significant differences between the groups.
Särkämö et al. (2010) <sup>31</sup>	54	Yes	Single	Favourite music and audiobook listening vs. standard care / Auditory sensory memory.	60 hours in 8 weeks	Listening to music and speech after neural damage can induce long-term plastic changes in early sensory processing.
Altenmüller et al. (2009) <sup>33</sup>	62	No	No	Children's music, folk songs, and tunes vs. conventional therapy / Neuroplasticity and motor recovery.	7.5 hours in 3 weeks	MST improved motor skills showed by ARAT score ( $p < 0.001$ , $d = 0.32$ ), Arm paresis score ( $p < 0.05$ , $d = 0.46$ ), Box and Block Test ( $p < 0.001$ , $d = 0.43$ ), and Nine Hole Pegboard Test ( $p < 0.05$ , $d = 0.32$ ).
Särkämö et al. (2008) <sup>32</sup>	54	Yes	Single	Favourite music and audiobook listening vs. standard care / Cognitive functions and mood.	60 hours in 8 weeks	Music listening improved verbal memory ( $p = 0.002$ , $d = 0.88$ ) and focused attention ( $p = 0.012$ , $d = 0.92$ ) compared to the audiobook and control groups. Music group also experienced less depression ( $p = 0.031$ , $d = 0.77$ ) and confusion ( $p = 0.045$ , $d = 0.72$ ) than the control group.
Jeong et al. (2007) <sup>34</sup>	33	No	No	RAS vs. referral information / Upper and lower limb mobility, mood, interpersonal relationships, and quality of life.	16 hours in 8 weeks	RAS improved range of ankle extension ( $p = 0.018$ , $d = 0.61$ ) and arm flexibility up ( $p = 0.001$ , $d = 0.99$ ) and down ( $p = 0.008$ , $d = 0.62$ ), mood ( $p = 0.017$ , $d = 0.03$ ), and increased frequency and quality of interpersonal relationships ( $p = 0.003$ , $d = 0.96$ ).
Schneider et al. (2007) <sup>35</sup>	40	No	No	Children's music, folk songs, and tunes vs. conventional therapy / Motor recovery.	7.5 hours in 3 weeks	Music group improved in speed, precision and smoothness of movements as well as motor control in everyday activities evaluated by ARAT ( $p < 0.001$ , $d = 0.36$ ), Arm paresis score ( $p < 0.05$ , $d = 0.42$ ), Box and Block Test ( $p < 0.001$ , $d = 0.69$ ), and Nine Hole Pegboard Test ( $p < 0.05$ , $d = 0.24$ ).
Thaut et al. (2007) <sup>36</sup>	78	No	Single	RAS vs. Neurodevelopmental therapy / Gait parameters.	7.5 hours in 3 weeks	RAS improved velocity ( $p = 0.006$ , $d = 2.13$ ), stride length ( $p < 0.001$ , $d = 1.50$ ), cadence ( $p < 0.001$ , $d = 1.82$ ), and symmetry ( $p = 0.049$ , $d = 0.83$ ).
Schauer et al. (2003) <sup>37</sup>	23	No	No	RAS vs. gait training without musical feedback / Gait parameters.	5 hours in 3 weeks	RAS improved gait velocity ( $p = 0.008$ , $d = 0.46$ ), stride length ( $p = 0.009$ , $d = 0.49$ ), cadence ( $p = 0.045$ , $d = 0.02$ ), symmetry ( $p = 0.008$ , $d = 0.55$ ), heel-toe distance ( $p = 0.006$ , $d = 0.40$ ).
Thaut et al. (1997) <sup>38</sup>	20	No	Single	RAS vs. physical therapy / Gait parameters.	30 hours in 6 weeks	RAS improved gait velocity ( $d = 1.45$ ), stride length ( $d = 0.93$ ), symmetry ( $d = 0.52$ ), and cadence ( $d = 0.44$ ).
16 studies	664					

	Number of participants	MT involved	Blinding	Study design / Primary outcome	Overall intervention time	Main results
DEMENTIA						
Sánchez et al. (2016) <sup>57</sup>	18	No	No	Multisensory stimulation vs. music listening / Neuropsychiatric symptoms and cognition.	16 hours in 16 weeks	Multisensory stimulation showed positive effects on anxiety symptoms and dementia severity that were not observed in the music group.
Särkämö et al. (2016) <sup>44</sup>	83	Yes	Single	Music listening and/or singing vs. standard care / Emotional parameters.	15 hours in 10 weeks	Both music listening and singing groups improved in behavioral disturbances ( $p = 0.04$ , $d = 0.42$ ) and physical signs ( $p = 0.008$ , $d = 0.52$ ) more than the control group: 6 months after the intervention, found effects were not present anymore.
Raglio et al. (2015) <sup>45</sup>	98	Yes	Single	Music therapy and music listening vs. standard care / Behavioral and psychological symptoms of dementia.	10 hours in 10 weeks	There were no significant differences between the groups.
Hsu et al. (2015) <sup>46</sup>	13	Yes	No	Music listening, singing, improvising and talking vs. standard care / Neuropsychiatric symptoms, well-being, and carer-resident interaction.	11 hours in 22 weeks	Music group showed improvement in symptoms ( $p = 0.002$ , $d = 2.32$ ) and in levels of wellbeing ( $p < 0.001$ , $d = 3.85$ ). Staff in the intervention group reported enhanced caregiving techniques as a result of the programme.
Särkämö et al. (2015) <sup>47</sup>	83	Yes	Single	Singing or music listening vs. standard care / Clinical, demographic, and musical background factors influencing the cognitive and emotional efficacy of caregiver-implemented musical activities.	15 hours in 10 weeks	Singing was beneficial especially in improving working memory in mild dementia and in maintaining executive function and orientation in younger PWDs. Music listening was beneficial in supporting general cognition, working memory, and quality of life especially in moderate dementia not caused by Alzheimer's disease (AD) who were in institutional care. Both music interventions alleviated depression especially in mild dementia and AD. The musical background of the PWD did not influence the efficacy of the music interventions.
Chu et al. (2014) <sup>58</sup>	100	Yes	Single	Group music therapy vs. standard care / Mood and cognition.	6 hours in 6 weeks	Group music therapy decreased depression ( $p = 0.001$ , $d = 0.21$ ) and delayed the deterioration of cognitive functions, especially recall ( $p = 0.004$ , $d = 0.72$ ). The effects were present 1 month after cessation of the intervention.
Vink et al. (2014) <sup>48</sup>	76	Yes	Single	Music therapy (listening and singing) vs. other activities / Neuropsychiatric symptoms.	21 hours in 16 weeks	Neuropsychiatric symptoms decreased significantly in the music therapy group ( $p = 0.01$ ).
Narme et al. (2014) <sup>49</sup>	37	-	Single	Music therapy (listening, playing and singing) vs. cooking / Patients' mood, cognition, behavioral disturbances, and on the and stress experienced by nurses.	8 hours in 4 weeks	There were no significant differences between the groups.
Särkämö et al. (2014) <sup>59</sup>	83	Yes	Single	Singing or music listening vs. standard care / Quality of life, mood and cognition.	15 hours in 10 weeks	Music listening improved the patients' mood ( $p = 0.001$ , $d = 0.80$ ), orientation ( $p = 0.005$ , $d = 0.71$ ), episodic memory ( $p = 0.036$ , $d = 0.54$ ) attention and executive functions ( $p = 0.039$ , $d = 0.48$ ), overall cognitive performance ( $p = 0.041$ , $d = 0.47$ ), and the quality of life ( $p < 0.001$ , $d = 0.99$ ). Singing resulted in additional improvement in short-term memory and working memory ( $p = 0.006$ , $d = 0.75$ ), and improved the caregiver wellbeing ( $p = 0.026$ , $d = 0.85$ ).
Vink et al. (2013) <sup>50</sup>	77	Yes	Single	Music listening and singing vs. other activities / Agitation.	21 hours in 16 weeks	There were no significant differences between the groups.
Ceccato et al. (2012) <sup>51</sup>	50	Yes	Single	Music therapy vs. standard care / Cognition and anxiety.	18 hours in 12 weeks	The music group improved performance in attention ( $p = 0.001$ , $d = 0.76$ ) and verbal episodic memory tasks (immediate $p = 0.001$ , $d = 0.76$ , delayed $p = 0.001$ , $d = 0.73$ ), but not in anxiety.
Sung et al. (2012) <sup>52</sup>	52	No	No	Favourite music vs. standard care / Anxiety.	6 hours in 6 weeks	Anxiety decreased in the music group ( $p = 0.004$ , $d = 0.06$ ).
Lin et al. (2011) <sup>53</sup>	100	Yes	No	Music therapy (playing and listening) vs. standard care / Agitation.	6 hours in 6 weeks	There were no significant differences between the groups.
Cooke et al. (2010) <sup>50</sup>	47	Yes	Single	Music therapy (listening and playing) vs. reading / Mood and quality of life.	32 hours in 16 weeks	There were no significant differences between the groups.
Raglio et al. (2010) <sup>54</sup>	60	Yes	Single	Music therapy vs. standard care / Behavioral disturbances.	6 hours in 4 weeks	Music reduced the behavioral disturbances showed by significant group difference ( $p < 0.05$ , $d = 0.63$ ).
Guétin et al. (2009) <sup>55</sup>	30	Yes	Single	Music therapy vs. resting and reading / Anxiety and mood.	5 hours in 16 weeks	Music therapy decreased anxiety ( $p < 0.001$ , $d = 2.42$ ) and depression ( $p = 0.002$ , $d = 1.05$ ). These effects persisted up to 2 months after stopping the intervention.

Raglio et al. (2008) <sup>56</sup>	59	Yes	Single	Music therapy vs. other activities / Behavioral and psychologic symptoms.	15 hours in 16 weeks	Music therapy improved behavioral symptoms (p < 0-0001, d = 1-04), functional ability (p < 0-0001, d = 0-79), and empathetic behavior (p < 0-0001, d = 0-61) compared to the control treatment.
17 studies	1066					

	Number of participants	MT involved	Blinding	Study design / Primary outcome	Overall intervention time	Main results
PARKINSON'S DISEASE (PD)						
Pohl et al. (2013) <sup>63</sup>	18	Yes	Single	Music listening, rhythmic clapping or stomping vs. standard care / Motor performance, cognition, quality of life	12 hours in 6 weeks	Music therapy improved mobility (p = 0·006), UPDRS (p = 0·003), Text re-call (p = 0·036), Item naming (p = 0·033), performance in Stroop test (p = 0·007), and Quality of life (p = 0·031).
de Bruin et al. (2010) <sup>64</sup>	22	No	Single	Favorite music synchronized to gait vs. regular activities / Walking parameters	19·5 hours in 13 weeks	Walking to music improved velocity (p = 0·002, d = 2·64), stride time (p = 0·019, d = 1·76), cadence (p = 0·007, d = 2·16), UPDRS (p = 0·002, d = 0·50).
Hackney et al. (2009) <sup>65</sup>	48	No	Single	Tango or waltz/foxtrot vs. standard care / Functional motor control.	20 hours in 13 weeks	Tango group improved in balance (p = 0·001, d = 2·98), 6-minute walking (p = 0·001, d = 2·50) and backward stride length (p = 0·001, d = 2·19) and Waltz/Foxtrot group in balance (p = 0·001, d = 3·17), 6-minute walking (p = 0·001, d = 2·24) and backward stride length (p = 0·018, d = 1·96).
Hackney et al. (2009) <sup>67</sup>	61	No	No	Tango and waltz/foxtrot vs. Tai Chi or standard care / Health-related quality of life.	20 hours in 13 weeks	Tango improved mobility (p = 0·03, d = 2·50), social support (p = 0·05, d = 2·97), and Quality of life (p < 0·01, d = 2·09).
Hackney et al. (2007) <sup>66</sup>	19	No	Single	Tango vs. physical exercise / Functional mobility.	20 hours in 13 weeks	Tango group improved in balance (p = 0·01, d = 2·18).
5 studies	168					

	Number of participants	MT involved	Blinding	Study design / Primary outcome	Overall intervention time	Main results
MULTIPLE SCLEROSIS (MS)						
Gatti et al. (2015) <sup>69</sup>	19	No	No	Keyboard playing vs. mute keyboard playing / Hand function.	7·5 hours in 2 weeks	The music group improved in the functional use of the hand significantly more showed by Time x Group interaction (p = 0·003, d = 0·60).
Conklyn et al. (2010) <sup>70</sup>	10	Yes	No	RAS vs. standard care / Gait parameters.	2 weeks	RAS significantly decreased double-support time (left: p = 0·018, d = 1·61; right: p = 0·025, d = 1·46).
2 studies	29					

	Number of participants	MT involved	Blinding	Study design / Primary outcome	Overall intervention time	Main results
EPILEPSY						
Bodner et al. (2012) <sup>73</sup>	73	No	Single	Nightly exposure of Mozart Sonata K. 448 vs. no intervention / Seizure occurrence.	Every night for 1 year	Music group significantly decreased in seizure frequency during the treatment phase (17%, p = 0·014) and even one year post-treatment (16%, p = 0·027).
1 study	73					

Effect size = mean pre-post change in the treatment group minus the mean pre-post change in the control group, divided by the pooled pre-test standard deviation.<sup>96</sup>

Effect size was defined small when d = 0-2, medium when d = 0-5 and large when d = 0-8.

d = Effect size, BATRAC = Bilateral arm training with rhythmic auditory cueing, MIT = Melodic Intonation Therapy, MST = Music-supported Therapy, MT = Music therapist, RAS = Rhythmic auditory stimulation.

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